IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	:	09/776,096
Applicant	:	Mark W. Perlin
Filed	:	February 2, 2001
Art Unit	:	1631
Examiner	:	Russell Scott Negin
Docket No.	:	PERLIN-9
Title of the Invention	:	Method and System for DNA Mixture Analysis

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Date: 6/9/14

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Signature: Ansel Schwartz

AMENDMENT

Sir:

In response to the Office Action of December 9, 2013, please amend the above-identified patent application as follows.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 15 of this paper.

EXHIBIT
3

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claim 1 (currently amended): A method of analyzing a DNA mixture comprised of the steps:

(a) obtaining a DNA mixture that contains genetic material from at least two contributing individuals;

(b) amplifying the DNA mixture in a DNA amplification process to produce an amplification product comprising DNA fragments;

(c) producing from the amplification product a signal comprising signal peaks from the DNA fragments;

(d) detecting signal peak amounts in the signal, and quantifying the amounts to produce DNA lengths and concentrations **[[**information**]]**from the mixture to form quantitative genotyping data;

(e) assuming a **[[**genoptype**]]**genotype value of alleles for a contributor to the quantitative genotyping data at a genetic locus;

(f) setting a mixture weight value for a relative proportion of the contributors to the quantitative genotyping data;

(g) forming a linear combination of the genotype values based on the mixture weight value;

(h) deriving with a computer a data variance of the amplification process from a model that includes both the quantitative genotyping data and the linear combination; and

(i) determining with the computer a probability of the quantitative genotyping data from the DNA mixture at the locus using both the linear combination and the data variance value.

Claim 2 (canceled)

Claim 3 (previously presented): The method as described in Claim 1 wherein the amplifying step at a locus generates relative amounts of DNA fragments that are proportional to relative amounts of DNA template present in the DNA mixture.

Claim 4 (previously presented): The method as described in Claim 3 wherein the detecting step generates relative amounts of signal that are proportional to the relative amounts of DNA fragments.

Claim 5 (currently amended): The method as described in Claim 1 wherein the forming step includes a mathematical operation based on a linear model that relates the quantitative genotyping data to a product of a genotype matrix multiplied by a weight vector that describes the relative contribution of each individual that is considered in the DNA mixture.

Claim 1 recited the limitation the "data" in step f and several times onwards, and had an insufficient antecedent basis. This limitation is now amended in the current invention to the more specific "quantifying DNA lengths and concentrations from the mixture to form quantitative genotyping data" without any reference to "information". "Quantitative genotyping data" is clearly formed in step d, and that phrase is now carried forward on that a sufficient antecedent basis in steps e, f, h and i. Moreover, that more precise language is now stated in the relevant dependent claims.

Claim 1, step h, was ambiguous because it was unclear whether the derived data variance was from the data itself, or from applying the linear combination to the data. This ambiguity has been clarified in step h, which now reads, "deriving ... a data variance ... from a model that includes both the quantitative genotyping data and the linear combination." The step now explicitly states that *both* the quantitative genotyping data *and* the linear combination are part of deriving the data variance.

Claim Rejections - 35 USC Sect. 103

Rejection #1

The examiner has rejected claims 1, 3-10, 23-27, 29-35, 39, 41-42 46-49, 51-54, and 56-58 as being unpatentable over Perlin et al (American Journal of Human Genetics, 1995) in view of Perlin et al (American Journal of Human Genetics, 1994), in view of Ballabio et al (Nature, 1990), in view of Mossa et al (EP, 1997. Applicant respectfully traverses this rejection in view of the amendments to the claims.

None of these teachings alone or in combination in any way make obvious the instant invention, as amended.

Claim 1, step e, as amended, clarifies that a genotype value for a contributor to the mixture is a "genotype value of alleles for a contributor". A genotype of a contributor is comprised of alleles, typically an *allele pair* at an autosomal STR locus. Examiner's cited prior art of Perlin et al (1995) refers to stutter deconvolution methods for either (a) determining a genotype allele pair for one individual, i.e., not for a contributor to a *mixture*, or (b) determining a set of pooled alleles, i.e., not separate and distinct genotype *allele pairs* for each contributor to a mixture. The instant invention determines the genotype alleles (e.g., allele pairs, with one allele inherited from each parent) for each contributor to a mixture, and is therefore distinguished from the prior art.

In this light, the stutter amplification matrix A in Perlin et al (1995; page 1201, column 2, paragraph 1, and figures 2 and 3) is seen to be entirely different from the genotype design matrix G in the published specification (paragraphs 34 and 48). Matrix A describes a linear stutter transformation of *alleles*, whereas G describes a set of allele *pair genotype* values for each individual contributing to a DNA mixture. Representing and eliminating allele stutter (matrix A) has an entirely different meaning and application than representing the genotype allele pair values of each individual in a mixture (matrix G).

Matrix A is not matrix G; they are conceptually, functionally, operationally and entirely distinct from each other. An allele is not a genotype. A set of pooled alleles is not the same as a set of individual genotypes. A large allele pool *merges* alleles so that individuals cannot be distinguished, whereas the present invention *separates* genotype allele pairs for different contributing individuals. The claimed invention separates individual genotypes in a novel way.

Claim 1, step h, as amended, clarifies that the data variance is derived from a model that includes *both* the quantitative genotyping data *and* the linear combination (of the genotype allele pair values based on the mixture weight value). In the notation of the specification, this means that the data variance depends on both the data d and the linear mixture combination G times w. There is no data variance in the prior art that depends on *both* the quantitative data d *and* a linear combination G*w of contributor genotypes G with contributor mixture weights w.

Claim 1, step i, as amended, clarifies that the probability of the quantitative DNA mixture data is determined using *both* the linear combination G*w *and* the data variance. One way of doing this is given in the specification (paragraph 192) where the probability of the data Pr{d|G,w} is given a probability distribution that explicitly includes linear combination G*w *and* the data variance in a multivariate normal distribution that contains all those parameters. There is no probability of quantitative mixture data (in statistics, the "probability of the data" is also referred to as a "likelihood") in the prior art that is determined using *both* the linear combination G*w and the data variance value.

In statistics, a likelihood ratio (LR) is a change in belief in a hypothesis based on observed data (J. Good, "Probability and the Weighing of Evidence", Chapter 6, 1950). The claimed invention describes a LR in the specification (paragraph 203). With regard to claim 47, there is nothing resembling a LR in the Appendix of Perlin et al (1994).

The cited prior art provides mechanisms for removing stutter from a set of alleles, whether individual or pooled. Claim 1 of the instant invention determines in step (i) a probability of DNA mixture data using a linear combination of genotype values and mixture weights, together with a data variance derived from the data and linear combination. Moreover, Claim 46 computes a genotype probability, separating an individual out of the mixture, using this

determined probability of data. This separation of individual genotypes with a probability description, as claimed, does not appear in the prior art.

Accordingly, claim 1 is patentable over the applied art of record. Claims 3-10, 23-27, 29-35, 39, 41-42 46-49, 51-54, and 56-58 are dependent to claim 1 and are patentable for the reasons claim 1 is patentable.

Rejection #2

The examiner has rejected claims 21-22 and 43-45 as being unpatentable over Perlin et al (American Journal of Human Genetics, 1995) in view of Perlin et al (American Journal of Human Genetics, 1994), Ballabio et al (Nature, 1990) in view of Mossa et al (EP, 1997) in view of Evett et al (Journal of Forensic Science, 1998).

Applicant respectfully traverses this rejection in view of the amendments to the claims. Claim 1 is patentable over the applied art of record, as discussed above in the "Rejection #1" section. Removing stutter from pooled alleles (prior art) is one problem. Determining genotype allele pair probabilities for individuals who have contributed their DNA to a mixture (claimed invention) is another problem. These are entirely different problems, and they have different solutions.

Claim 1 is patentable over the applied art of record. Claims 21-22 and 43-45 are dependent to claim 1 and are patentable for the reasons claim 1 is patentable.

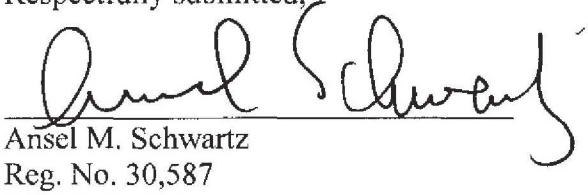
Rejection #3

DNA identification is the forensic gold standard. Criminal justice uses DNA evidence to identify, prosecute, defend, convict and exonerate suspected criminals. However, hundreds of thousands of DNA items are mixtures that contain two or more individuals. Crime laboratories often cannot properly interpret their mixture data, and so this crucial evidence is significantly underreported, or discarded altogether as "inconclusive".

As supported by the Declaration of Dr. Perlin filed herewith, the claimed invention solves the DNA mixture problem by providing more accurate match statistics. This accuracy has been established through scientific validation and is accepted by courts. The claimed invention has introduced reliable DNA identification information in criminal proceedings where none previously existed. By making better use of DNA data, the claimed invention helps society convict the guilty, free the innocent, and protect the public from crime.

In view of the foregoing amendments and remarks, it is respectfully requested that the outstanding rejections and objections to this application be reconsidered and withdrawn, and Claims 1, 3-10 and 21-83, now in this application be allowed.

Respectfully submitted,



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